Caffeine enhances memory function after cholinergic blockade

group were withdrawn from the study due to raised LFTs or adverse events. No serious sequelae resulted from these. One patient in the placebo group and two patients in the tacrine group died from causes which were considered unrelated to the treatment.

Conclusion: Tacrine produced an improvement that was detected by a physician and the patient's carer. Overall psychometric scores did not change, but more patients did better on tacrine than placebo. The clinical relevance of these findings varied considerably among patients. Doses over 80mg tacrine per day may be more effective in patients who can tolerate tacrine.

410

CHRONIC LOW DOSE EPTASTIGMINE IN ALZHEIMER PATIENTS: RELATIONSHIP BETWEEN ACETYLCHOLINESTERASE INHIBITION AND COGNITIVE EFFECTS. B.P. Imbimbo, P.E. Lucchelli. Medical Dept., Mediolanum Farmaceutici, Milan, Italy.

Eptastigmine is a long acting acetylcholinesterase (AChE) inhibitor. A double-blind, placebo-controlled, multicenter study assessed the safety, tolerability, pharmacodynamics and preliminary efficacy of multiple oral doses of eptastigmine in 100 patients with mild to severe Alzheimer's disease. Patients were randomly assigned to eptastigmine (30-60 mg/day) or placebo for 4 weeks at a ratio of 4:1. Red blood cell AChE activity was repeatedly measured from 10 µL capillary blood with an automated device. Nine patients dropped out mainly due to uncooperativeness. No hematological adverse events occurred. Nineteen patients on eptastigmine had cholinergic adverse events associated to peak AChE inhibition exceeding 50% after the first dose or 70% at steady-state. Four patients had a modest reversible increase in liver enzymes. Thirty-two patients who completed an 8-week open extension phase with the drug did not show any significant decrease in neutrophil counts. At steady-state, the mean of individual maximum values of AChE inhibition was 54 ± 2% and was reached after 3.1 ± 0.6 days. Trough inhibition of AChE activity increased during the first four days of treatment, reaching a mean value of 23 ± 2% at Day 4 which remained constant throughout the study period (25 ± 1% at Day 29). Mean recovery half-life of enzyme activity was 7.5 ± 0.9 h. Overall, 31% of the patients improved on eptastigmine according to the Physician Clinical Global Impression of Change versus 0% of the patients on placebo ($p<0.05$). Fifty percent of a patient subgroup with 25-35% steady-state AChE inhibition showed clinical improvement. Performance on both word fluency and logical memory tasks improved with an inverted U-shaped relation to average steady-state AChE inhibition. This study indicates that daily doses of eptastigmine up to 60 mg per day are well tolerated and safe even after prolonged treatment. Moderate steady-state AChE inhibition is associated to maximal cognitive and clinical improvement.

411

CLINICAL AND NEUROPHYSIOLOGICAL EVALUATION OF 3 DOSES OF S12024 (50, 100, 200 mg o.d.) DURING REPEATED ORAL ADMINISTRATION (7 days) IN 12 OUT-PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE.

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The cognitive enhancing properties of S12024, which appears to facilitate noradrenergic and vasopressin activity, have been shown for the acquisition and recall aspects of memory in marmoset, monkeys and aged rats. Four randomized placebo-controlled studies have demonstrated good clinical and laboratory tolerability in volunteers (up to a single 600 mg dose in 90 young and up to 400 mg/d in 45 elderly during 7 days) and in Alzheimer's patients (n=87) up to 400 mg/d during 28 days, with preliminary evidence of memory enhancement at 200 mg/d according to 2 computerized cognitive assessment systems.

The objective of this study was to obtain early evidence that S12024 has potential central pharmacological activity and cognition enhancing properties in out-patients with mild to moderate Alzheimer's disease. The trial was a monocenter, randomized, placebo-controlled study of latin square design, with 3 oral doses of S12024-2 (50, 100, 200 mg o.d.), administrated during 4 double-blind treatment periods of 7 days, each separated by a 2-week wash-out period. The cognitive evaluation criteria were MMS, Clinician Interview Based on Impression of Change (CIBIC), the Van Der Linden battery of memory and attentional assessments (VDL), and family evaluation scales of daily activities. Cognitive testing was performed at the selection visit (training session), at the inclusion visit D0 (prior to the first intake as the baseline) and 1.5 hour after the first intake at D1 and after the last intake at D7 of each period. Quantitative EEG (during a closed eye test session) and event related potential (ERP) (during a selective auditory attention task) were also performed at D7 of each period.

Twelve patients (mean age: 64 years old +/- 10, mean MMS: 23 +/- 3) completed the study. No treatment effect was observed for MMS, VDL battery or activities of daily living scores. A significant period effect was shown at day 1 and day 7 between the second and the 4th period of treatment for some items in favor of a learning effect (implicit memory). CIBIC results showed a non significant treatment effect in favor of active treatment (100>200>50>0). Significant change was observed in qEEG β1 and δ signals at 200 mg versus placebo ($p=0.01$) in favor of nonspecific stimulation of vigilance. A significant difference ($p<0.05$) was shown between placebo and S12024 concerning the amplitude of the ERP PN signal ("processing negativity"), indicating central pharmacodynamic activity without dose-effect relations.

In summary, S12024 has shown preliminary evidence of central pharmacodynamic activity predominantly at 200 mg/d based on neurophysiological assessments results in favor of some influence on vigilance or attention in patients with AD. Good clinical and biological tolerability was demonstrated by the parameter stability. The on-going European phase IIb study on 300 AD patients treated during 3 months will provide more data.

412

PHARMACODYNAMIC EFFECTS OF REPEATED ORAL ADMINISTRATION OF 4 DIFFERENT DOSES OF S12024-2 (Cognitive Enhancer) IN 36 HEALTHY ELDERLY VOLUNTEERS. K. Wesnes**, E. Neuman*, H.J.G. de Wilde***, M. Malbezin*, H.J.M.J. Crijns***, J.H.G. Jonkman***, D. Guez*.

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The cognitive potential enhancing properties of S12024, which appears to facilitate the activity of brain noradrenalin and vasopressin, have been found to enhance the acquisition and recall of information in marmoset, monkey and aged rats.

In order to determine whether any evidence of similar effects could be obtained in man, the Cognitive Drug Research (CDR) computerized assessment system was included in a placebo-controlled double blind, rising dose, tolerance and pharmacokinetic trial of the compound in 36 elderly (> 60 years) volunteers.

The trial was conducted in five sequential stages, in each, 6 volunteers received active and 3 placebo medication over 7 days. The doses administered in the four stages were twice daily 10, 50, 100 and 200 mg S12024-2 respectively. After 4 training sessions, cognitive testing was performed prior to the morning dosing and then at 1.5, 3, 4.5 and 8 hours post-dosing on days 1 and 6. The pre-dosing score on day 1 was used as the baseline. The CDR system included assessments of simple and choice reaction time, sustained vigilance, memory scanning and delayed recognition of words, picture and faces.

Comparison of the pre-dosing performance of this elderly population to that of young control volunteers identified a clear pattern of slowed performance on the various attentional and memory tasks. When compared to placebo, S12024 produced a dose-dependent improvement in the speed of recognition performance at the intermediate doses (50 and 100 mg t. d.) and to a lesser extent at the 200 mg dose level; 10 mg dose was ineffective.

In conclusion, this study has shown preliminary evidence that S12024-2 is capable of correcting age related declines in human cognitive processes in a dose-dependent fashion. The study highlights the advantage of including appropriate cognitive early in the process of drug evaluation and is promising for the development of S12024-2 as a cognition enhancer. Further work on the compound is underway to confirm and extend these findings (eg. Allain et al, Derouesné et al., this conference).

413

CAFFEINE ENHANCES MEMORY FUNCTION AFTER CHOLINERGIC BLOCKADE. W. Riedel, R.L.A.M. Leboux, E. Hogervorst, A. Quist, A. van der Vusse, F.R.J. Verhey and J. Jolles. Academic Psychiatric Centre, Dept. of Psychiatry & Neuropsychology, University of Limburg, P.O. Box 616, 6200 MD Maastricht, The Netherlands.

A great number of clinical trials have been conducted to assess the efficacy of newly developed cognition enhancers in the treatment of Alzheimer's Disease as well as Age-Associated Memory Impairment. Nevertheless, research has only shown minor effects of newly developed substances that should enhance cognition. One of the world's most widely used cognitive enhancers is caffeine. A large postal survey conducted by our department, among 2043 normal subjects divided over 13 age groups ranging from 25-85 years yielded that the subjects' reported average daily coffee consumption is low in the youngest age group (3 cups /day), gradually increases with age and peaks at 50 yrs (5 cups /day), remains constant until 75 yrs (4 cups /day) and diminishes in the two highest age groups (3 cups /day).

Nicotine and possibly also caffeine play a protective role in the development of dementia. Nicotine's ability to reverse the scopolamine-induced cognitive dysfunction has been demonstrated previously, but caffeine's hasn't. Sixteen healthy volunteers in the age range of 25-40 years were medically screened and treated in accordance with the declaration of Helsinki. They received, on 3 separate occasions, weight calibrated doses of 0.5 mg / 75 kg scopolamine s.c., followed one hour later by the double-blind, double-dummy placebo-controlled administration of either 2 mg nicotine in chewing gum, 250 mg caffeine in coffee (3 cups), or placebo. Subjects performed a test battery consisting of measures of

perceptual and psychomotor speed, information processing, primary and secondary memory, memory scanning and focussed and divided attention, at 1 hour before and 2, 4 and 6 hours after scopolamine administration. The first analysis of the performance data shows that scopolamine produced severely disturbed memory as well as psychomotor functions. Caffeine significantly diminished the impairing effect of scopolamine in the memory tasks. Especially secondary memory and delayed recognition parameters were improved after caffeine relative to scopolamine alone. This led to the conclusion that (disturbed) memory storage, but not retrieval, was positively affected by caffeine. Psychomotor performance was not affected by caffeine. The effects of nicotine were minor and were less than expected on the basis of previously reported studies. Analysis of blood levels can possibly lead to an explanation.

As far as we know, this is the first demonstration of caffeine's potential to selectively enhance memory functioning in subjects who suffer from scopolamine-induced cholinergic dysfunction. Taking into account that caffeine also antagonizes hang-over effects of benzodiazepines and that cholinergic dysfunction is one of the manifestations of Alzheimer's Disease, it can be concluded that caffeine consumption might be helpful in preventing or postponing the symptoms of Alzheimer's Disease.

414

THERAPY WITH A COMBINATION OF IRON, VITAMIN B6 AND COENZYME Q10 IN THE LONG TERM FOR SPORADIC ALZHEIMER'S DISEASE. Masaki Imagawa MD. Department of Neuropsychiatry, Hyogo Prefectural Amagasaki Hospital, Hyogo, Japan.

Of the theraphy with combination of coenzyme Q10 (CoQ10), vitamin B6 and iron, two in the same family were found to have mis-sense mutation of amyroid β-protein precursor gene'. This therapy have been tried in 20 patients with the sporadic Alzheimer's disease (AD) in the long term (one year). It is suggested that this therapy may be effective for AD. SUBJECTS AND METHODS This clinical study included 20 AD, mean ± SD age, males 61.8 ± 6.8 y.o., females 61.8 ± 6.8 y.o., 20 patients have been suffered from AD from 1 year to 7 years. Diagnosis was based on DSM- III -R. Mental stage and daily activity were evaluated with mini-mental state examination scors (MMSE) and functional assessment staging (FAST). And so the clinical course was followed by the two methods. These numbers have changed according to the severity of the patient's symptoms and signs. Theses scales were marked on the time scale (0, 2 weeks, 1, 3, 6 months, one year). The dose of the drugs taken by the patients was iron 50-150 mg, B6 90-180 mg, CoQ10 60-180 mg, daily. RESULTS In this therapy, each points have significantly different from zero point in scores. In MMSE, 0: 14.6 ± 7.0 (n=20), 2W: 22.5 ± 5.4 (n=16)*, 1M: 20.3 ± 5.4 (n=18)*, 3M: 21.5 ± 5.4 (n=20)*, 6M: 20.3 ± 7.1 (n=20)*, 1Y: 21.6 ± 6.5 (n=11)*. *, paired t test, p<0.001. In FAST, the stage have changed from 5 stage (zero point) to 3 stage. DISCUSSION Why dose this therapy effect in AD? In general, iron, particularly the action of Fe* have a intoxication in vivo because of free radicals. But iron is essential mineral on the body, especially, brain. Adding to CoQ10, iron dependent free radicals may be disappeared. In this therapy it is focus on the production of the neurotransmitters through the decarboxylation (B6 B6-enzyme) with ATP. B6 is acquires the biosynthesis of GABA. Neuronal cell's death said to be the hypothesis of glutamine iduced cell's death. Therefore, it is importance that the action of B6 is related with GABA shunt.

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415

NEW POSSIBILITIES IN THE TREATMENT OF PATIENTS WITH ALZHEIMER DISEASE. S.A. Groppa, Department of Neurology and Neurosurgery, Medical University, Kishinev 277072 Moldova.

The effect of the drug, dimethylsulfoxid, was studied in 18 patients with "probable AD" diagnosed according to NINCDS-ADRDA criteria. Patients were repeatedly tested for a period of 9 months. Efficacy was estimated from the results of neurological and neuropsychological testing, immunological examination of neurospecific proteins (NSP) and autoantibodies (AAB) to them.

The obtained results indicated that the severity of mental-amnestic disturbances and disorientaiton in time and space reliably decreased after 3 and especially 6 months of treatment. There was also a trend for praxic and speech impairments to decrease from baseline. In addition, indices of concentration and communicability improved.

The results of immunoenzyme analysis of NSP and AAB to them showed a decrease of NSP serum concentration and a stabilizing influence of dimethylsulfoxid on the blood-brain barrier.

The action mechanism, clinical efficacy and adverse reactions will be discussed.

416

CARDIOVASCULAR SAFETY AND HORMONAL BEHAVIOUR IN DEMENTED ELDERLY PATIENTS TREATED WITH POSATIRELIN. SHORT TERM STUDY. D. Cucinotta, S. Costantini, R. Del Buono, L. Ambrosoli* and R. Girardello* Geriat. Med. S.Orsola-Malpighi University Hospital, Bologna * Res. Dev. Dept. POLI Industria Chimica S.p.A., Milan - Italy

Posatirelin (L-pyro-2-aminoadipyl-L-leucil-prolinamide) is a synthetic neuropeptide with neurotrophic activity and modulatory effects on various neurotransmission systems.

This drug is to-day under study in many clinical trials in Europe, according to results obtained in preliminary studies in patients suffering from dementia, either of Alzheimer type or vascular origin.

This double-blind, randomized, short-term clinical trial was carried out in order to evaluate the safety profile of *Posatirelin* on both cardiovascular and hormonal parameters.

24 hrs non invasive ambulatory blood pressure, cardiac frequency monitoring and EKG recording (for 5 minutes) in 20 patients with dementia (mild to moderate degree) were determined before and after treatments. 10 patients underwent *Posatirelin* (10 mg daily i.m., 8 days) and 10 placebo treatment according to a randomization code. GH release, T_3, T_4, TSH and PRL levels and routine laboratory parameters were determined at baseline and at the end of treatment. 9 males and 11 females (65-80 yrs, mean ± SD: 75.10 ± 3.7; MMSE score 12-21, mean ± SD: 16.35 ± 2.5) entered and completed the study.

Behaviour of cardiovascular parameters did not show significant difference comparing *Posatirelin* to placebo. Similarly, no changes in the EKG were recorded. No significant changes (out of normal biological variability) in haematological, serum chemistry or urinanalysis were observed. GH concentration/time curves, T_3, T_4, TSH and PRL levels changes were statistically not significant and unrelated to treatment.

At the end of the treatment (60 minutes after injection) higher values of TSH and PRL in *Posatirelin* group than in placebo group were observed. This findings have to be verified in further studies, but it is necessary to take into consideration that variability was within normal range of values.

The results of this study suggest that *Posatirelin* may be proposed as a safe drug for the treatment of demented elderly patients.

417

CENTRAL SEROTONERGIC HYPERRESPONSIVITY IN ALZHEIMER'S DISEASE. D.M.McLoughlin, J.V.Lucey and T.G.Dinan. Institute of Psychiatry, London SE5 8AF, and Dept. of Psychiatry, Trinity College Medical School, Dublin 8, Ireland.

A wide range of neuroanatomical and biochemical deficits have been identified in the central serotonergic (5-HT) system in Alzheimer's disease (AD). In order to investigate the functional significance of these abnormalities the prolactin (PRL) response to the 5-HT specific neuroendocrine probe *d*-fenfluramine (*d*-FEN) was measured in 9 patients with late-onset probable AD (NINCDS-ADRDA criteria) and in an elderly healthy comparison group. PRL levels were measured hourly for 5 hours following an oral dose of 30mg of *d*-FEN. The PRL response to *d*-FEN (Δ PRL) was calculated by subtracting the baseline PRL from the maximum PRL level post ingestion of *d*-FEN. There was no significant difference in baseline PRL levels between the two groups and the peak PRL response occurred in all subjects within 300 mins. The mean ΔPRL in the AD group was 209.6(SD=116.9) mU/l and 95.8(SD=53.4) mU/l in the comparison group. The Δ PRL response was significantly greater in the AD group (Z=2.04, df=16, p=0.04; Mann-Whitney U test).

This preliminary study is the first to report an enhanced 5-HT neuroendocrine responsivity in late-onset AD. 5-HT abnormalities have been implicated in depression, anxiety and impulsive, aggressive behaviour. 5-HT has also been recognised as having an influence, possibly inhibitory, on learning and memory. The finding of a functionally hyperresponsive 5-HT system in AD could provide a rationale for the use of 5-HT antagonists for the management of behavioural and cognitive symptoms in AD.

418

MANAGING PROBLEM BEHAVIORS ASSOCIATED WITH ALZHEIMER'S DISEASE: A PIAGETIAN APPROACH. M.A. Matteson, A. Linton, M.J. Lichtenstein, B. Cleary. University of Texas Health Science